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| SERIAL NUMBER | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---------------|-------------|----------------------|---------------------|
| 07/566,977 | 08/13/90 | COOK | 1515-23 |

CROUCH EXAMINER

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ART UNIT 1864 PAPER NUMBER

10/23/91

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on SEP 5 1991 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 1 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 13-24 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 13-24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable, ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner, ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved, ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTO-1556
(5/87)

The first Office Action failed to identify the species elected by applicant. Examiner regrets the omission of the species election in the first office action. Applicant is requested to affirm the election of species 2' deoxyfuranosyl halogen and phosphorothioate substitutions.

This application contains claims directed to the following patentably distinct species of the claimed invention: H, OH, halo, azido, amino, thioalkoxyl, haloalkoxyl, alkyl sulfide, alkyl sulfonate, nitrate, nitrite, ammonium, allyloxy, alkeneoxy, or methoxy substitution of the 2'-deoxyfuranosyl and phosphorothioate, methyl phosphonate or phosphate alkylate substitution of the phosphate.

During a telephone conversation with Mr. John Caldwell on April 25, 1991 a provisional election was made with traverse to prosecute the invention of group III, claims 13-24, species 2' deoxyfuranosyl halogen and phosphorothioate substitutions. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-12 and 25-36 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant's election without traverse of group III in Paper No. 7 is acknowledged.

Applicant's arguments filed September 5, 1991 in paper no. 7 have been fully considered but they are not deemed to be persuasive. The amendment has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 13-24 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification in the first office action. Claims 13-24 are directed towards a method for modulating the production of a protein in an organism by antisense oligonucleotides. It is agreed that applicant has demonstrated that in an aqueous assay system that the oligonucleotides taught by applicant hybridize. However applicant has not demonstrated that said anti-sense

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oligonucleotides have an effect on modulating protein production in an intact organism. The inhibition of protein synthesis within a cell or intact organism is not a routine next step procedure. Applicant must teach that the invention functions as claimed. The effective amount of antisense oligonucleotide administered is not at issue here.

Claims 13-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons stated in the previous office action. Applicant's stated intent to claim all organisms is objected to in view of the lack of enablement of any organism.

Claims 13-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Ikehera in view of Marcus-Sekura. Applicant's argument that because Marcus-Sekura found one method to inhibit nuclease attack on anti-sense oligonucleotides an artisan would not be motivated to combine with the teachings of Ikehera of a second modification to inhibit nuclease attack on oligonucleotides is not convincing. Marcus-Sekura teaches a modification where phosphorothioate replaces the normal phosphate and Ikehera teaches a halogen substitution of the 2' deoxyfuranosyl moiety of the nucleotide. These modifications are distinct. The use of one modification is not excluded by the use

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of the other. Applicant states that Ikehera teaches that the 2' deoxyfuranosyl halogen substitutions have a destabilizing affect on the thermal stability of the molecule. Additionally, the temperatures at which the thermal transition points were made are not at physiological temperatures. The lowest temperature where measurements were made, 46°C, would be lethal to cells or organisms; 46°C is the equivalent of about 113°F. Furthermore, one negative teaching does not negate the entire teaching in view of Ikehera stating that these changes in thermal stability have little affect on conformation such that the 2' halogen substituted oligonucleotides retain biological activity.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-4216.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dr. D. Crouch
October 21, 1991

Elizabeth C. Weimar
ELIZABETH C. WEIMAR
SUPERVISORY PATENT EXAMINER
ART UNIT 184